



## **Clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome an international consensus statement**

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## OPEN

### EXPERT CONSENSUS DOCUMENT

# Clinical and molecular diagnosis, screening and management of Beckwith–Wiedemann syndrome: an international consensus statement

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**Abstract** | Beckwith–Wiedemann syndrome (BWS), a human genomic imprinting disorder, is characterized by phenotypic variability that might include overgrowth, macroglossia, abdominal wall defects, neonatal hypoglycaemia, lateralized overgrowth and predisposition to embryonal tumours. Delineation of the molecular defects within the imprinted 11p15.5 region can predict familial recurrence risks and the risk (and type) of embryonal tumour. Despite recent advances in knowledge, there is marked heterogeneity in clinical diagnostic criteria and care. As detailed in this Consensus Statement, an international consensus group agreed upon 72 recommendations for the clinical and molecular diagnosis and management of BWS, including comprehensive protocols for the molecular investigation, care and treatment of patients from the prenatal period to adulthood. The consensus recommendations apply to patients with Beckwith–Wiedemann spectrum (BWSp), covering classical BWS without a molecular diagnosis and BWS-related phenotypes with an 11p15.5 molecular anomaly. Although the consensus group recommends a tumour surveillance programme targeted by molecular subgroups, surveillance might differ according to the local health-care system (for example, in the United States), and the results of targeted and universal surveillance should be evaluated prospectively. International collaboration, including a prospective audit of the results of implementing these consensus recommendations, is required to expand the evidence base for the design of optimum care pathways.

Beckwith–Wiedemann syndrome (BWS) is a multisystem human genomic imprinting disorder with variable clinical expression and complex molecular aetiology<sup>1</sup>. BWS is an overgrowth syndrome, with patients often presenting with macroglossia, abdominal wall defects, hemihyperplasia (lateralized overgrowth), enlarged abdominal organs and an increased risk of embryonal tumours during early

childhood. BWS is caused mainly by genetic or epigenetic defects within the chromosome 11p15.5 region<sup>2</sup>. This region contains imprinted genes, such as *CDKN1C* and *IGF2*, which are strong regulators of fetal growth. Although BWS might present prenatally or in adult life, it is most commonly diagnosed in the neonatal period or in early childhood, with an estimated prevalence of 1 affected child

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per 10,340 live births<sup>3</sup>. Since the first descriptions half a century ago, a PubMed search (conducted on 15 November 2016) for “Beckwith Wiedemann”, “Wiedemann Beckwith” or “EMG syndrome” yielded >1,500 BWS-related articles. However, clinical practice varies regarding the diagnosis and care of individuals with BWS.

To address these issues, the European Cooperation in Science and Technology (COST)-funded European Network for Congenital Imprinting Disorders initiated

a BWS consensus programme that involved an extensive literature review, preparation and critical appraisal of draft documents and a final face-to-face consensus meeting involving invited experts and patient group representatives. This effort produced a series of consensus recommendations for the diagnosis and care of individuals with the newly defined Beckwith–Wiedemann spectrum (BWS<sub>p</sub>), which are presented in this Consensus Statement.

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## Methods

A PubMed search using the keywords “Beckwith Wiedemann”, “Wiedemann Beckwith” or “EMG syndrome” yielded articles of interest that were selected on the basis of the abstracts, with particular consideration given to the number of patients included and the description of the molecular mechanisms. Only articles mentioning the molecular mechanisms were retained. Articles were then reviewed by at least two experts and sorted into three groups: clinical diagnosis (group 1); molecular diagnosis (group 2); and clinical management (group 3).

The international BWS consensus group comprised 41 participants from 36 institutions across 11 countries, predominantly based in Europe, including clinicians, clinical and research scientists and patient group representatives with expertise in different aspects of BWS (clinical and molecular geneticists, paediatric endocrinologists, oncologists, orthopaedists, oro-facial surgeons and nephrologists). A modified Delphi consensus process was adopted<sup>4</sup>. Discussions occurred via conference calls, email communications and file exchanges. Two face-to-face meetings were held: a preliminary meeting of 11 participants (including one patient group representative) in February 2016 to identify the key issues to be addressed by the consensus group and a plenary 3-day meeting involving 35 participants (including 2 patient group representatives) in March 2017. During this plenary meeting, experts participated in one of the three subgroups (clinical, molecular or management) on the basis of their field of expertise, discussed the draft consensus documents and formulated and voted on the consensus recommendations (BOX 1). This Consensus Statement summarizes the outcome of these discussions and is divided into three subject areas: clinical aspects; molecular aspects; and care and management.

## Clinical aspects of BWS

Since the seminal descriptions by Beckwith<sup>5</sup> and Wiedemann<sup>6</sup> in the 1960s, there have been many attempts to define BWS by use of various clinical criteria that have been reported with different prevalences in cohorts of BWS ([Supplementary information S1](#) (table)); however, no agreed clinical definition of BWS has emerged. Since the findings in the 1990s of molecular abnormalities of chromosome 11p15.5 in BWS<sup>7–9</sup>,

it has been recognized that these genetic and epigenetic changes are frequently mosaic and lead to a range of clinical phenotypes. These include ‘classical BWS’ (OMIM #130650), which is characterized by macroglossia, anterior abdominal wall defects and prenatal and postnatal overgrowth, among other symptoms ([Supplementary information S1](#) (table)), and some cases of isolated lateralized overgrowth (previously called ‘isolated hemihypertrophy’ or ‘isolated hemihyperplasia’; OMIM #235000)<sup>10</sup> in addition to patients with a chromosome 11p15.5 molecular anomaly who do not fit into these first two groups, a condition termed ‘atypical BWS’ by this consensus group. Given the overlapping phenotypes and common molecular mechanisms between these groups, the consensus group decided that these phenotype and/or genotype combinations could be best classified as parts of the BWSp (TABLE 1, R1) and that the recommendations of this consensus should be applied to individuals with BWSp (FIG. 1; TABLE 1).

## Clinical features of BWSp

BWS has classically been characterized by macroglossia, macrosomia, abdominal wall defects and an increased risk of embryonal tumours<sup>11–17</sup>. There is growing recognition that not all patients with BWS display all of these phenotypic features and that patients have remained undiagnosed because they did not present with one of these features, such as macrosomia, which was initially considered as a cardinal feature but is present in only one-half of the patients with an 11p15.5 molecular defect<sup>18,19</sup>. The clinical features outlined as part of the consensus BWSp scoring system include features that, when present, are more likely to lead to a positive diagnosis (termed ‘cardinal features’), including macroglossia, exomphalos, lateralized overgrowth, multifocal Wilms tumour or nephroblastomatosis, hyperinsulinism and specific pathology findings (such as adrenal cytomegaly or placental mesenchymal dysplasia) (BOX 2). Macrosomia has been defined according to different criteria in different clinical cohorts<sup>11–13,15–17</sup>, making it challenging to assess the role it has as a cardinal feature. Lateralized overgrowth is the novel term for hemihypertrophy (or hemihyperplasia), which is defined as asymmetric overgrowth of part of the body<sup>10</sup>. Embryonal tumours such as Wilms tumours and hepatoblastoma can occur outside of the diagnostic scope of BWSp; however, multifocal Wilms tumours are more likely to occur in BWSp. As a cardinal feature, hyperinsulinism is defined as prolonged hypoglycaemia in the context of elevated insulin levels that last >1 week and/or require escalated treatment<sup>20</sup>, while transient hypoglycaemia resolves without the need for further intervention. Although pathology findings cannot always be evaluated (especially when BWSp is not suspected prenatally or at birth and when placental samples are not collected), the diagnosis of BWSp should be considered in cases of adrenal cortex cytomegaly, placental mesenchymal dysplasia and pancreatic adenomatosis<sup>5</sup>. Additionally, if samples are available (especially from the placenta after birth) and the diagnosis is being considered, pathological investigation can be beneficial in making the clinical diagnosis.

### Box 1 | Details of the consensus voting process

For voting on individual recommendations, participants ( $n=33$ ) selected from the following options (patient group representatives did not vote):

- A. Evidence or general agreement allow full agreement with the recommendation
- B. Evidence or general agreement are in favour of the recommendation
- C. Evidence or general agreement are weak for the recommendation
- D. There is not enough evidence or general agreement to agree with the recommendation

Depending on the proportion of votes received, the strength of the recommendation was recorded as follows:

- +, 26–49% of the votes
- ++, 50–69% of the votes
- +++, ≥70% of the votes

Table 1 | Consensus recommendations of the clinical working group

R	Recommendation	Strength of recommendation
<b>BWSp scoring system and clinical indications for molecular testing for BWS</b>		
1	BWSp is usually caused by dysregulation of the chromosome 11p15 imprinted region and involves overgrowth in multiple tissues, often in a mosaic state. BWSp encompasses a range of phenotypes, and children might present with one or more features (summarized in BOX 2). Classical BWS and lateralized overgrowth ('hemihypertrophy and/or hemihyperplasia') are considered subsets of the BWSp (FIG. 1). A third subset is defined as patients with an 11p15 anomaly who do not fit into these first two groups	A+++
2	There have been many proposed systems to define classical BWS, which have suggested combinations of macroglossia, omphalocele/exomphalos and/or (asymmetric) overgrowth. Although often associated, increased height and/or weight (macrosomia) are no longer considered a cardinal feature of BWS. For simplicity and consistency, we have developed consensus criteria (TABLE 2): a score of $\geq 4$ must be reached for a diagnosis of classical BWS. Children who meet these criteria would be considered to have BWSp, even if an 11p15 anomaly is not identified	A+++
3	BWSp lateralized overgrowth is defined as a marked increase in the length and/or girth of most or all of one side of the body compared with its contralateral side in addition to an 11p15 abnormality. A child with an 11p15 anomaly who does not meet the criteria for classical BWS or BWSp lateralized overgrowth is still considered to be part of the BWSp. There are currently insufficient data to determine the management guidelines for patients with lateralized overgrowth without an identified 11p15 anomaly in tested samples; this group falls outside the scope of this consensus	A+++
4	We recommend molecular testing in anyone suspected of being in the BWSp (lateralized overgrowth, classical BWS or features in TABLE 2). For simplicity, we recommend molecular testing for any patient with $\geq 2$ points. In cases where isolated omphalocele and/or exomphalos is present, testing can be considered at the discretion of the physician. Testing is also recommended with a family history of a parent with heritable pathogenic 11p15 anomaly, which places the child at a 50% risk of being affected. First tier testing is blood lymphocyte DNA	A+++
5	Hypoglycaemia is defined as plasma glucose levels $< 50$ mg/dl for the first 6 hours of life and $< 60$ mg/dl thereafter. Hyperinsulinism is defined as a glucose infusion rate of $\geq 8$ mg/kg/min, a detectable level of insulin and/or C-peptide and undetectable levels of ketones and free fatty acids. Transient hypoglycaemia as a suggestive feature is defined by the above criteria lasting $< 1$ week. Hyperinsulinism as a cardinal feature is defined by these criteria lasting $> 1$ week and/or requiring escalated treatment	A++
<b>BWS and ART</b>		
6	There is an established association between ART and BWS. The absolute risk of BWS in an individual conceived by ART is estimated to be very low (no more than 1 in 1,000). Additional research is required to further characterize this association and the relationship between subfertility, hormonal stimulation, embryo manipulation and imprinting defects	A+++

ART, assisted reproduction technology; BWS, Beckwith–Wiedemann syndrome; BWSp, Beckwith–Wiedemann spectrum.

Features characterized as 'suggestive features' are likely to occur independently in the general paediatric population and are therefore given less weight in the consensus BWSp scoring system outlined in the next section. Suggestive features include a birthweight greater  $> 2$  standard deviation scores (SDS), facial naevus flammeus, polyhydramnios or placentomegaly, ear creases or pits, transient hypoglycaemia, embryonal tumours, nephromegaly or hepatomegaly and umbilical hernias or diastasis recti.

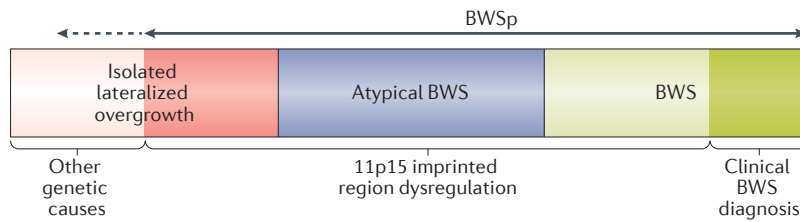
### Consensus scoring system and definition

The many previously proposed systems to define BWS have suggested various combinations of clinical features (with macroglossia, exomphalos and/or (asymmetric) overgrowth as major features)<sup>11–13,18,21,22</sup> with the aim of optimizing the likelihood of a classical and molecularly confirmed diagnosis. Frequently cited and recent phenotype articles from the past 25 years were reviewed for the prevalence of individual clinical features (Supplementary information S1 (table)), which were then classified as cardinal or suggestive features (BOX 2). As several of these articles referenced the same patient cohorts<sup>12–16,18,21–26</sup>, data were analysed from the nine articles describing apparently distinct cohorts<sup>11,12,14,15,18,21,23,25,26</sup>. The goal of this BWSp scoring system (TABLE 1; BOX 2) was to recognize that BWS falls into a clinical spectrum and that some features that

have long been considered to be classical parts of the syndrome are not present in every patient, and therefore, the diagnosis should not be dismissed owing to the absence of such features. Additionally, this Consensus Statement sought to include elements that could be pathognomonic for BWS. In addition to informing the presence of a diagnosis of classical BWS, the consensus group also determined that the same system could be used to provide guidance regarding when to pursue genetic testing. We compared this new scoring system with previously published systems (Supplementary information S2 (figure)) while keeping in mind that previous systems focused on the diagnosis of classical BWS and molecularly confirmed BWS and not the diagnosis of the BWSp.

Cardinal features are considered key to the clinical diagnosis, whereas suggestive features add to the likelihood of a clinical diagnosis and the indications for molecular testing but are less specific (BOX 2). Cardinal and suggestive feature designations were analysed in the BWSp cohort reported by Ibrahim *et al.*<sup>11</sup> and were shown to be largely superior to previous diagnostic systems (Supplementary information S2 (figure)). Limitations of the study were that transient hypoglycaemia versus prolonged hyperinsulinism were not typically distinguished in the prior cohorts, so this feature could therefore not be assessed, and that macrosomia was variably defined in previous cohorts<sup>11–14,17,18,21,22</sup>.





**Figure 1 | The Beckwith–Wiedemann spectrum.** The consensus group introduced the concept of the Beckwith–Wiedemann spectrum (BWSp), which includes patients with a clinical diagnosis of Beckwith–Wiedemann syndrome (BWS) with or without an (epi) genetic change at the BWS locus on chromosome 11p15, patients with ‘atypical BWS’ (defined as fewer cardinal and suggestive features than those needed for a clinical diagnosis of BWS) and an (epi)genetic change at the BWS locus, and patients with ‘isolated lateralized overgrowth’ and an (epi)genetic change at the BWS locus. The dotted arrow indicates that some patients with apparent isolated lateralized overgrowth and no 11p15 abnormality might subsequently be found to have an 11p15 abnormality on testing of additional tissues or with a more sensitive assay. Patients with clinical BWS and no detectable 11p15 abnormality might be further investigated with additional clinical evaluation and consideration of other syndromes, which may have features overlapping with BWSp, and appropriate testing for those syndromes may be warranted.

Cardinal features include macroglossia, exomphalos, lateralized overgrowth, multifocal Wilms tumour, prolonged hyperinsulinism and distinct pathologic findings that are unique to BWS. The major differences between the consensus and previous scoring systems are the classification of macrosomia and hyperinsulinism. Although it is often associated with BWSp, macrosomia (defined as height and/or weight  $>2$  SDS) is no longer considered a cardinal feature, as it is variably defined in previous cohorts and it might be present in only approximately one-half of patients with BWS<sup>16,26</sup>. Hyperinsulinism (defined in TABLE 1, R5) without another identifiable molecular cause can be the initial presenting feature of BWSp<sup>27,28</sup>. Hyperinsulinism is classified as a cardinal feature when lasting  $>1$  week and requiring escalated treatment and as a suggestive feature when lasting  $<1$  week.

For simplicity and consistency, we have developed consensus criteria by use of cardinal and suggestive features (TABLE 1, R2). For a clinical diagnosis of classical BWS, a patient requires a score of  $\geq 4$  based on cardinal and suggestive features; this clinical diagnosis does not require the molecular confirmation of an 11p15.5 anomaly. Patients with a score of  $\geq 2$  (including those with classical BWS with a score of  $\geq 4$ ) merit genetic testing according to our algorithm for investigation and diagnosis of BWS (FIG. 2). Patients with a score of  $<2$  do not meet the criteria for genetic testing. Patients with a score of  $\geq 2$  with negative genetic testing should be considered for an alternative diagnosis and/or referral to a BWS expert for further evaluation.

Clinical diagnosis within the BWSp beyond the clear diagnosis of classical BWS or a clear molecular diagnosis is challenging and requires a combination of molecular testing and physician opinion. There is currently not enough published data to provide clear clinical recommendations for patients with a score of  $<4$  who have no molecular abnormality. Nonetheless, patients with a cardinal feature of BWS (such as macroglossia, hyperinsulinism, a multifocal Wilms tumour or a pathological finding) should be referred to a specialist with expertise

in BWS for further evaluation. Patients with isolated exomphalos are more common and are less likely to have an 11p15.5 defect compared with patients with other isolated symptoms, and should therefore not be included in the BWSp. Lateralized overgrowth can occur both as a symptom of BWSp and independent of BWSp<sup>10</sup>. When lateralized overgrowth occurs with an 11p15 abnormality, it is considered part of BWSp. As there are multiple molecular causes of lateralized overgrowth aside from 11p anomalies (for example, *PIK3CA* and *AKT1* mutations), lateralized overgrowth without an 11p15 anomaly in a child who does not meet the criteria for classical BWS was considered to be outside the BWSp and the scope of this Consensus Statement; thus, recommendations for further investigation and clinical management were not made (TABLE 1, R3).

### Indications for molecular testing

The consensus group recommended that molecular testing is indicated in patients with a score of  $\geq 2$  (BOX 2) unless there is an alternative explanation (for example, gestational diabetes mellitus for macrosomia) (TABLE 1, R4). For isolated exomphalos, molecular testing is discretionary. Testing is recommended in patients with a family history and a known heritable pathogenic 11p15 anomaly (a positive family history might occur in 10–15% of patients<sup>2,29</sup>). Some features included in some previous diagnostic criteria (for example, cleft palate, advanced bone age, polydactyly and supernumerary nipples) are suggestive of an alternative diagnosis such as Simpson–Golabi–Behmel syndrome<sup>30</sup> and are therefore not included in the consensus scoring system. Although renal abnormalities are common in patients with BWSp, they are usually present with other features and not as an isolated feature. When molecular testing is negative, other relevant disorders should be considered in the differential diagnosis (FIG. 2; see [Supplementary information S3](#) (table)).

### Assisted reproduction technology

Assisted reproductive technologies (ARTs) are defined as treatments handling male and female gametes outside of the body and include procedures such as *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI)<sup>31</sup>. ARTs account for 1–3% of all births in industrialized countries<sup>31</sup>. Although these techniques are regarded as safe, it has been suggested that the establishment and/or maintenance of DNA methylation at imprinted loci might be disturbed by ART<sup>31–36</sup>. Following reports of children with a rare molecular subtype of Angelman syndrome who were conceived by ICSI<sup>32,33</sup> and an increased frequency ( $\sim 4$ – $6$ -fold) of ART births in children with BWS<sup>34–36</sup>, a population-based study estimated the risk of BWS in IVF-conceived children to be approximately 1 in 4,000, substantially greater than that in the general population<sup>31</sup>. A study from 2017 reported a tenfold increased risk of BWS with ART but an absolute risk of approximately 1 in 1,000 (REF. 37). Although some epidemiological studies have not detected an increased relative risk of BWS in children born after ART<sup>38,39</sup>, molecular studies support an association, as  $>90\%$  of children with BWS conceived by

## Box 2 | Clinical features of Beckwith–Wiedemann spectrum

### Cardinal features (2 points per feature)

- Macroglossia
- Exomphalos
- Lateralized overgrowth
- Multifocal and/or bilateral Wilms tumour or nephroblastomatosis
- Hyperinsulinism (lasting >1 week and requiring escalated treatment)
- Pathology findings: adrenal cortex cytomegaly, placental mesenchymal dysplasia or pancreatic adenomatosis

### Suggestive features (1 point per feature)

- Birthweight >2 SDS above the mean
- Facial naevus simplex
- Polyhydramnios and/or placentomegaly
- Ear creases and/or pits
- Transient hypoglycaemia (lasting <1 week)
- Typical BWSp tumours (neuroblastoma, rhabdomyosarcoma, unilateral Wilms tumour, hepatoblastoma, adrenocortical carcinoma or pheochromocytoma)
- Nephromegaly and/or hepatomegaly
- Umbilical hernia and/or diastasis recti

For a clinical diagnosis of classical Beckwith–Wiedemann syndrome (BWS), a patient requires a score of  $\geq 4$  (this clinical diagnosis does not require the molecular confirmation of an 11p15 anomaly). Patients with a score of  $\geq 2$  (including those with classical BWS with a score of  $\geq 4$ ) merit genetic testing for investigation and diagnosis of BWS. Patients with a score of  $< 2$  do not meet the criteria for genetic testing. Patients with a score of  $\geq 2$  with negative genetic testing should be considered for an alternative diagnosis and/or referral to a BWS expert for further evaluation. BWSp, Beckwith–Wiedemann spectrum; SDS, standard deviation scores.

ARTs have an epimutation at the centromeric imprinting centre *KCNQ1OT1*:transcriptional start site (TSS) differentially methylated region (DMR) (also known as IC2), compared with  $\sim 50\%$  of children with BWS who were not conceived by ART<sup>40</sup>. Various factors might contribute to an association between ARTs and Angelman syndrome or BWS, including infertility *per se* (that is, independently to ART techniques)<sup>41,42</sup>, superovulation or *in vitro* embryo culture<sup>43–45</sup>. The link between ART and epigenetic defects has also been suggested by the large offspring syndrome (an ART-associated phenomenon in sheep and cows that has some phenotypic similarity to BWS), which has been reported to be associated with epigenetic alterations similar to those observed in BWS<sup>46</sup>. However, although there is clear evidence linking ARTs and BWS, additional research is required to further elucidate the relationships between subfertility, hormonal stimulation, embryo manipulation and imprinting defects (TABLE 1, R6).

### Molecular aspects of BWSp

BWSp is associated with molecular abnormalities affecting a cluster of imprinted genes located within the chromosome region 11p15.5–11p15.4, which is divided into two functionally independent domains: the centromeric and telomeric domains<sup>2</sup> (FIG. 3). Each domain harbours its own imprinting control region, marked by a DMR. The insulin-like growth factor 2 (IGF2)-encoding gene (*IGF2*) and the gene encoding the non-translated long non-coding RNA (lncRNA) *H19* are located in the telomeric domain and are controlled by the *H19/IGF2*:intergenic (IG) DMR (also known as imprinting control

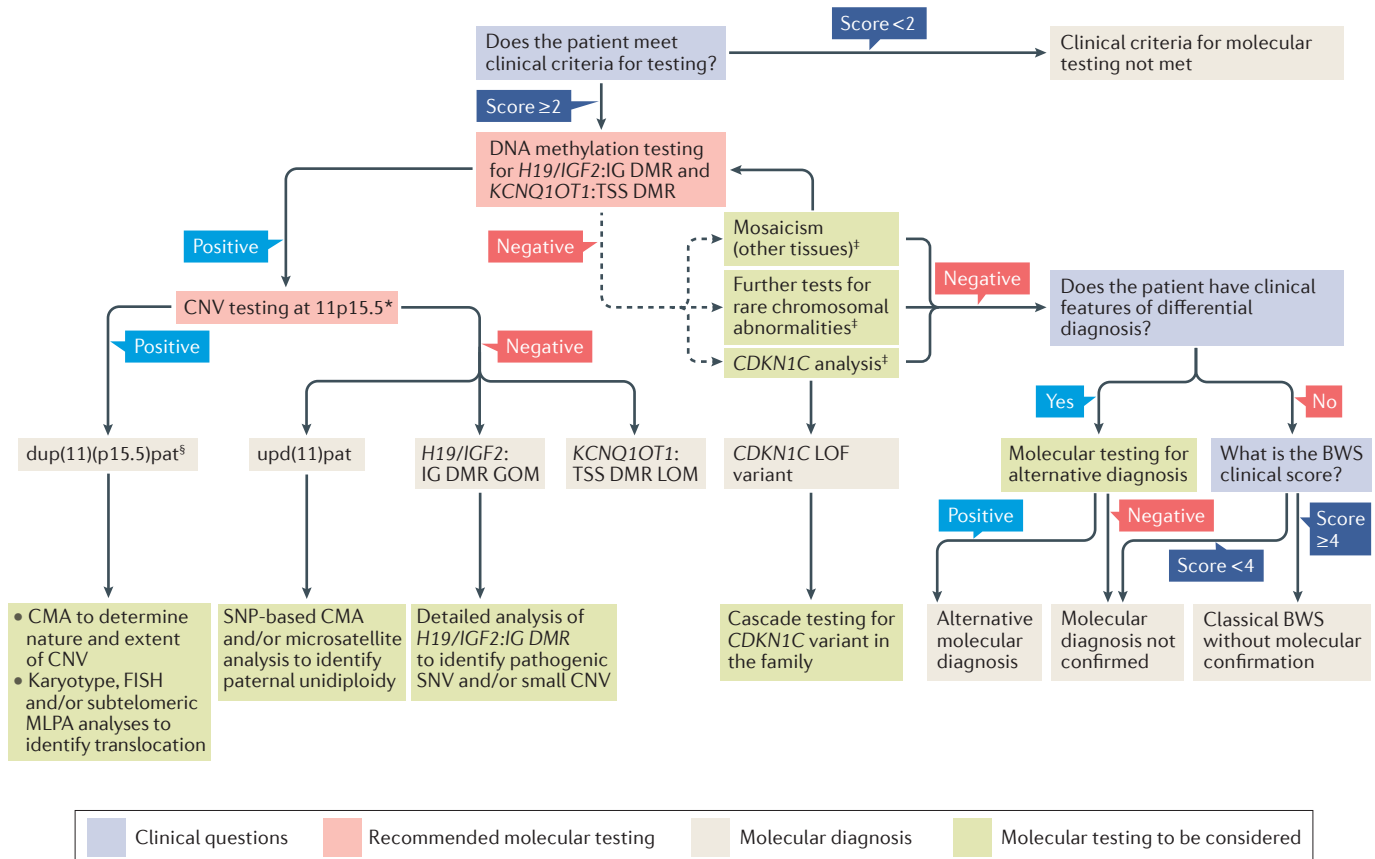
region 1 (ICR1), *H19*-DMR or Imprinting Centre 1 (IC1); OMIM \*616186). The cell cycle inhibitor gene *CDKN1C* and the gene encoding the regulatory lncRNA *KCNQ1OT1* are located in the centromeric domain and are controlled by the *KCNQ1OT1*:TSS DMR (also known as KvDMR, *LIT1*-DMR, imprinting control region 2 (ICR2) or Imprinting Centre 2 (IC2); OMIM \*604115). The Human Genome Variation Society (HGVS)-recommended nomenclature, *H19/IGF2*:IG DMR and *KCNQ1OT1*:TSS DMR, should be adopted in publications and test reporting<sup>47</sup> (TABLE 2, R7); however, for brevity, IC1 and IC2 are used hereafter.

A molecular defect affecting imprinted genes in chromosome region 11p15 can be demonstrated in  $\sim 80\%$  of patients with BWSp<sup>2</sup>. DNA methylation abnormalities are the most frequent defects; loss of methylation (LOM) at the maternal IC2 allele is found in  $\sim 50\%$  of patients and gain of methylation (GOM) at the maternal IC1 allele in 5–10% of patients<sup>48</sup>. Mosaic, segmental paternal uniparental isodisomy (UPD) of 11p15.5 (commonly referred to as segmental upd(11)pat) can be detected in 20% of patients, intragenic *CDKN1C* mutations can be detected in 5% of sporadic and 40% of familial cases, and chromosomal abnormalities in 11p15 can be detected in  $< 5\%$  of patients<sup>2</sup>. The frequency of twinning is markedly higher in patients with BWS than the general population; in the majority of cases, twins are female, monozygous and discordant (that is, one twin is affected and one is unaffected by BWSp)<sup>49</sup>. Owing to the sharing of circulation during development, DNA from blood cells or saliva might show aberrant DNA methylation (usually IC2 LOM) in both affected and unaffected discordant twins, whereas methylation is concordant with phenotype in non-blood-derived samples such as buccal swab<sup>50</sup>. Thus, buccal swab is the preferred source of DNA for unambiguous diagnosis in cases of discordant monozygotic twins.

### Molecular genetic testing for BWSp

A flowchart summarizing the molecular diagnostic pathway for investigation of suspected BWSp is presented in FIGURE 2 (TABLE 2, R8).

First-line molecular testing procedures should assay IC1 and IC2 methylation (TABLE 2, R9). Methylation is abnormal in cases of IC2 LOM, IC1 GOM, copy number variations (CNVs) and segmental upd(11)pat (both IC2 LOM and IC1 GOM)<sup>51</sup>. Abnormal methylation status confirms a diagnosis of BWSp, but its underlying mechanism must be established to define management, genetic counselling and recurrence risks<sup>48,51</sup>. Thus, if methylation is assayed using a technique that does not estimate DMR copy number, this should then be determined in all patients with IC1 and/or IC2 methylation abnormalities (FIG. 2). Currently, methylation-specific (MS) multiplex ligation-dependent probe amplification (MS-MLPA) is the most common diagnostic test, as it simultaneously detects DMR methylation status and copy number; however, other techniques (such as MS-PCR and MS quantitative PCR) are more sensitive in patients with low-level mosaicism (for a detailed list, see REFS 51–54 and the references within).



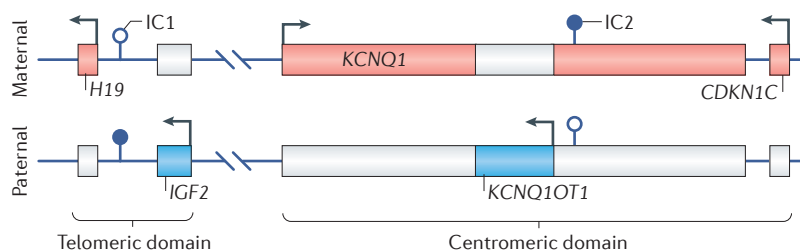
**Figure 2 | Flowchart for investigation and diagnosis of Beckwith-Wiedemann syndrome.** The figure summarizes the molecular diagnostic pathway for investigation of suspected Beckwith-Wiedemann spectrum (BWS). Patients with clinical features reaching a score of  $\geq 2$  should be genetically tested. It is recommended that first-line testing should assay the methylation status of *H19/IGF2*:intergenic (IG) differentially methylated region (DMR) (also known as IC1) and *KCNQ1OT1*:transcriptional start site (TSS) DMR (also known as IC2). If not estimated simultaneously with DNA methylation, DMR copy number should then be determined in all patients with IC1 and/or IC2 methylation abnormalities. These assays can yield positive molecular diagnosis of BWS with IC2 loss of methylation (LOM), IC1 gain of methylation (GOM), segmental paternal uniparental isodisomy (UPD) of 11p15.5 (upd(11)pat) or copy number variation (CNV; most commonly duplication of paternal 11p15.5 (dup(11)(p15.5)pat)). Further molecular tests can be considered to determine underlying mechanism of

methylation abnormality, UPD or CNV. If DNA methylation testing is negative, further molecular tests can be considered to identify mosaic methylation abnormalities, pathogenic *CDKN1C* variants or rare balanced chromosomal rearrangements. If all molecular tests are negative, differential diagnosis should be considered. However, a diagnosis of classical Beckwith-Wiedemann syndrome (BWS) is made in the presence of a clinical score of  $\geq 4$  even in the absence of the molecular confirmation of an 11p15 anomaly. CMA, chromosome microarray analysis (can be oligonucleotide-based and/or single-nucleotide-polymorphism-based platforms); FISH, fluorescence *in situ* hybridization; LOF, loss of function; MLPA, multiplex ligation-dependent probe amplification; SNP, single nucleotide polymorphism; SNV, single nucleotide variation. \*CNV status may be determined simultaneously with methylation testing. <sup>†</sup>See main text for indications for testing. <sup>‡</sup>Deletion of maternal 11p15.5 (del(11)(p15.5)mat) may be detected with lower frequency.

**Recommended investigations if testing for methylation abnormalities is positive.** If a DMR CNV is implied using a PCR-based methodology (such as MS-MLPA), chromosome microarray analysis (such as oligonucleotide polymorphism-based or single nucleotide polymorphism (SNP)-based arrays) should be considered to determine the nature and extent of the deletion or duplication, and karyotyping, fluorescence *in situ* hybridization or subtelomeric MLPA should be considered to identify possible chromosomal translocations<sup>54–57</sup>. Testing can then be extended to other family members as appropriate. A SNP-based array will also allow detection of uniparental disomy (and indeed mosaicism) if a CNV is not detected.

If IC1 GOM and IC2 LOM are detected without evidence of CNV, mosaic segmental upd(11)pat is probable and can, if necessary, be confirmed using microsatellite analysis or SNP-based chromosome microarray analysis<sup>58–61</sup>. SNP-based chromosome microarray is considered to be the most sensitive method to investigate low-level mosaic (for example, 1–5%) segmental upd(11)pat<sup>59</sup>. Mosaic paternal unidiploidy (that is, genome-wide paternal UPD) affects up to 10% of patients with uniparental disomy and, as mosaic paternal unidiploidy is associated with additional clinical features and an increased risk of tumour development, further investigations (SNP array or microsatellite analysis) to detect this molecular abnormality should be considered<sup>62–67</sup> (TABLE 2, R10).





**Figure 3 | The Beckwith–Wiedemann syndrome locus at chromosome 11p15.5.** The figure depicts the chromosome 11p15.5–11p15.4 region with the imprinted genes and control regions that are implicated in the pathophysiology of Beckwith–Wiedemann spectrum (BWS). The BWS locus can be divided into two functionally independent domains, the telomeric and centromeric domains. Each domain harbours its own imprinting control region that is differentially methylated on the maternal and paternal chromosomes. The insulin-like growth factor 2 (IGF2)-encoding gene (*IGF2*) and the gene encoding the non-translated long non-coding RNA *H19* are located in the telomeric domain and are controlled by the *H19/IGF2*:intergenic (IG) differentially methylated region (DMR) (also known as IC1), which is methylated on the paternal chromosome. The cell cycle inhibitor gene *CDKN1C* and the gene encoding the regulatory long non-coding RNA *KCNQ1OT1* are located in the centromeric domain and are controlled by the *KCNQ1OT1*:transcriptional start site (TSS) DMR (also known as IC2), which is methylated on the maternal chromosome. Genes expressed from the maternal chromosome are depicted as red boxes, and genes expressed from the paternal chromosome are depicted as blue boxes. Grey boxes indicate non-expressed alleles. Filled lollipops indicate methylated imprinting centres (ICs), and open lollipops indicate unmethylated ICs. Bent arrows indicate the orientation of transcription.

Up to 20% of patients with IC1 GOM might carry small CNVs in the DMR, which cannot be detected using chromosome microarray analysis, or single nucleotide variations (SNVs) in octamer-binding protein 4 (OCT4; also known as POU domain, class 5, transcription factor 1) or transcription factor SOX binding sites; these CNVs and SNVs are associated with a high risk of recurrence<sup>68–74</sup>. Although some small CNVs can be detected using MS-MLPA, detection of SNVs would require additional investigations that are unavailable in most diagnostic laboratories (TABLE 2, R11). However, targeted IC1 sequencing can be considered in a specialized laboratory if MS-MLPA shows IC1 GOM and no CNV, especially if there is a family history of BWS.

IC2 LOM is the most common epigenetic finding in BWS, but IC2 DMR deletions are rare<sup>55</sup>, and at present, there is no indication for analysing patients with BWS and IC2 LOM for SNVs. Approximately one-third of patients with IC2 LOM have multilocus imprinting disturbance (MLID)<sup>75–78</sup>. In most patients, the clinical importance of MLID is uncertain, and therefore, routine testing for MLID is not usually indicated; however, in patients with IC2 LOM and a family history of BWS and no IC2 DMR CNV, MLID testing might help to determine if further testing for *trans*-acting mutations should be considered<sup>79,80</sup>.

**Recommended investigations if first-line molecular testing is negative.** A negative result for first-line molecular testing for IC1 and IC2 methylation does not exclude BWS for a variety of reasons, including the possibility of low-level mosaicism that is below the limit of detection of methylation testing, a *CDKN1C* mutation, a rare balanced chromosomal rearrangement (for example, inversion and/or translocation), an unrecognized or

undetected cause of BWS (~20% of patients with a characteristic BWS phenotype remain without a molecular diagnosis<sup>2</sup>) or an incorrect clinical diagnosis (TABLE 2, R12–15). Further molecular testing should be prioritized according to the most probable cause; for example, a less severe phenotype with lateralized overgrowth would suggest mosaicism, whereas a classical BWS phenotype with an abdominal wall defect and a positive family history would indicate a potential *CDKN1C* mutation.

Mosaicism for the molecular defect occurs in most sporadic cases of BWS, and different tissues might have different proportions of affected cells<sup>81</sup>. First-line diagnostic testing is usually performed using blood-leukocyte DNA, and IC1 or IC2 methylation level might be equivocal or within the normal range. Analysis of DNA from buccal swabs, cultures of fibroblasts or cells of mesenchymal origin (for example, obtained from surgical resection and/or excision of hyperplastic tissues) improve the detection rate for all mosaic defects<sup>51,54,81</sup> (TABLE 2, R13).

*CDKN1C* mutations account for ~5% of sporadic cases of BWS and for 40% of familial cases (in the case of maternal inheritance)<sup>48,82</sup>. Detection of a candidate pathogenic *CDKN1C* variant enables appropriate cascade testing to clarify familial recurrence risks<sup>82,83</sup>. Rare cases of apparently *de novo* *CDKN1C* mutations can arise in siblings, presumably resulting from maternal germline mosaicism<sup>83</sup>.

Rare maternally inherited balanced translocations or inversions involving chromosome region 11p15 might or might not be associated with IC2 methylation anomalies and should be considered if first-line testing is negative<sup>84–87</sup> (TABLE 2, R14). Finally, when molecular testing is negative, other relevant disorders should be considered as differential diagnoses (FIG. 2; TABLE 2, R15; see [Supplementary information S3](#) (table)).

## Multilocus imprinting disturbance

MLIDs are those with altered DNA methylation in addition to the lesion responsible for the primary clinical presentation<sup>88</sup>. MLID has a higher prevalence in BWS than in other imprinting disorders, and genome-wide analyses have revealed MLID in approximately one-third of patients with BWS who have IC2 LOM but not in patients with segmental upd(11)pat or IC1 GOM<sup>48,75–78,81,88–91</sup>. In BWS, MLID almost exclusively involves loci methylated in the maternal, and not the paternal, germ line, although rare cases show LOM at both IC2 and IC1 (the latter finding is a feature of the growth restriction disorder Silver–Russell syndrome (SRS))<sup>76,92</sup>.

Rare cases of BWS-MLID have been associated with biallelic maternal-effect genetic mutations in *NLRP2* (REF. 79) and *NLRP5* (REF. 80) (which encode NACHT, LRR and PYD domains-containing protein 2 (NLRP2) and NLRP5), and therefore, the possibility of an underlying *trans*-acting genetic mutation in these genes may warrant consideration in genetic counselling.

Perhaps owing to the various methylation alterations and frequent mosaicism seen in MLID, its effect on the BWS clinical phenotype remains unclear<sup>75,76,78,89,92,93</sup>, and therefore, routine clinical diagnostic testing is not a recommendation of this consensus.

Table 2 | Consensus recommendations of the molecular working group

R	Recommendation	Strength of recommendation
<b>Molecular genetic analysis</b>		
7	Molecular genetic testing should be performed by a health professional experienced in the field of imprinting disorders. Recommended nomenclature (for example, HGVS) should be adopted in publications and in test reporting	A+++
8	The flowchart outlined in FIG. 2 should be followed for molecular diagnosis of BWSp	A+++
9	First-line molecular testing should include DNA methylation analysis of the <i>H19/IGF2</i> :IG DMR (IC1) and <i>KCNQ1OT1</i> :TSS DMR (IC2) regions. If a DNA methylation defect at either or both DMRs is found, further tests should be performed to identify possible underlying CNV or upd(11)pat (if it was not discriminated in initial diagnostic testing)	A+++
10	Given the different tumour spectrum associated with mosaic genome-wide paternal uniparental disomy, further testing should be considered to distinguish this condition from upd(11)pat	A+++
11	Detailed analysis of the <i>H19/IGF2</i> :IG DMR should be considered in individuals with GOM of this region, as SNVs and/or small CNVs can occur in these patients and confer high risk of recurrence (prioritized in the presence of a positive family history)	A+++
12	In patients with a negative methylation test result, second-line molecular testing should be considered and might include sequencing of the coding exons and the exon–intron boundaries of <i>CDKN1C</i> (prioritized in the presence of a positive family history, a cleft palate or an abdominal wall defect (umbilical hernia or exomphalos))	A+++
13	In patients with a negative methylation test result, second-line molecular testing should be considered and might include analysis of additional tissues to detect somatic mosaicism (prioritized in the presence of asymmetric overgrowth)	A+++
14	In patients with a negative methylation test result, second-line molecular testing should be considered and might include further tests for rare chromosomal rearrangements	A+++
15	In patients with a negative methylation test result, second-line molecular testing should be considered, and might include re-evaluation of the clinical diagnosis and reconsideration of differential diagnoses	A+++
16	Genetic counselling should be performed by a health professional experienced in the field of imprinting disorders	A+++
17	As the recurrence risk associated with genetic defects (for example, <i>CDKN1C</i> loss of function variants, CNVs and DMR SNVs) is dependent on their size, location and parental origin, these factors should be taken into consideration during counselling for the family	A+++
<b>Prenatal molecular genetic analysis</b>		
18	Prenatal molecular diagnostic investigations should be considered if prenatal ultrasonography reveals potential features of BWSp and should lead to a specific diagnosis (or exclude other potential conditions); they should also be considered if a positive family history with a known molecular defect is present, which would influence the management of the relevant pregnancy	A+++
19	The flowchart indicated for postnatal testing (FIG. 2) is not necessarily applicable to prenatal testing. Modification of this flowchart depends on the individual setting (for example, known molecular defects and specific clinical features)	A+++
20	Prior to offering prenatal diagnosis for BWSp, a detailed discussion of the technological limitations and ethical issues should be undertaken with the parents; in particular, they should be made aware that a normal result does not necessarily exclude the diagnosis	A+++
21	It is recommended that centres offering prenatal diagnosis prospectively collect information on the true/false positive/negative diagnostic rates and that this information is contributed to multicentre audits to enable best practice guidelines to be further developed and refined	A+++

BWSp, Beckwith–Wiedemann spectrum; CNV, copy number variation; DMR, differentially methylated region; GOM, gain of methylation; HGVS, Human Genome Variation Society; SNV, single nucleotide variant; upd(11)pat, segmental paternal uniparental isodisomy of 11p15.5.

### Recurrence risks in BWSp

The risk of recurrence for BWSp depends on the genetic aetiology and nature of any genetic or epigenetic defect identified as well as its parental origin. It is therefore recommended that family counselling should be performed by an individual experienced in the field of imprinting disorders and should take into account the precise nature of the anomaly detected (TABLE 2, R16,17).

It has been reported that up to 10–15% of cases of BWSp are familial and most commonly result from *CDKN1C* mutations, chromosome 11p15 abnormalities and genetic alterations within IC1 (REFS 2,29). In these cases, the mode of inheritance is autosomal dominant, but the recurrence risk is dependent on the sex of the parent transmitting the affected allele (TABLE 2, R17; TABLE 3).

Pathogenic *CDKN1C* variations have a 50% recurrence risk with variable expressivity if the mutation is inherited from the mother<sup>82,83</sup>. In principle, all 11p15 CNVs and balanced translocations have a 50% recurrence risk with phenotypes dependent on the parental origin<sup>54,84,86,87</sup>. In cases with paternal duplication of 11p15 resulting from the unbalanced segregation of a translocation or an inversion, individuals carrying the balanced rearrangement have a normal phenotype<sup>94</sup>. In some pedigrees, either BWSp or SRS has been observed depending upon paternal or maternal transmission of the 11p15 duplication<sup>57,95,96</sup>. Paternal transmission of a duplicated telomeric domain and maternal transmission of a deleted centromeric domain also usually result in BWSp with a high recurrence risk<sup>52,95,97,98</sup>. Prediction of

Table 3 | Summary of Beckwith–Wiedemann spectrum molecular defect categories and recurrence risk

Molecular defect	Frequency of molecular defect	Mosaicism observed	Risk of recurrence	Characteristic clinical features (compared with other molecular subgroups)
IC1 GOM	5% <sup>48</sup>	Yes <sup>27,54,76,78,81</sup>	<ul style="list-style-type: none"> <li>• If no genetic anomaly is present, &lt;1%<sup>2</sup></li> <li>• If genetic anomaly (for example, pathogenic SNV of copy number variant in the DMR) is present, 50%; dependent on parental origin<sup>71,73,105,106</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Low frequency of exomphalos<sup>11,14,17</sup></li> <li>• High risk of Wilms tumour<sup>14,58,149</sup></li> </ul>
IC2 LOM	50% <sup>48</sup>	Yes <sup>27,54,76,78,81</sup>	<ul style="list-style-type: none"> <li>• If no genetic anomaly is identified, &lt;1%<sup>2</sup></li> <li>• If a cis-acting genetic anomaly is present, 50%; dependent on parental origin<sup>99–103</sup></li> </ul>	<ul style="list-style-type: none"> <li>• High frequency of exomphalos<sup>11,14,17</sup></li> <li>• Low risk of Wilms tumour<sup>14,58,149</sup></li> </ul>
upd(11)pat	20% <sup>48</sup> (see also paternal unidiploidy)	Yes <sup>27,54,61,76,78,81</sup>	<1% <sup>2</sup>	<ul style="list-style-type: none"> <li>• High incidence of lateralized overgrowth<sup>11,14</sup></li> <li>• Low frequency of exomphalos<sup>11,14,17</sup></li> <li>• High risk of Wilms tumour and hepatoblastoma<sup>14,58,149</sup></li> </ul>
Loss-of-function CDKN1C variants	5% (40% in familial cases) <sup>48</sup>	Usually no but has been reported rarely <sup>83</sup>	50% on maternal transmission <sup>82,83</sup>	<ul style="list-style-type: none"> <li>• High frequency of exomphalos<sup>11,14,17</sup></li> <li>• Low risk of Wilms tumour<sup>14,58,149</sup></li> </ul>
dup(11)(p15.5) pat	~2–4% <sup>55</sup>	No <sup>55</sup>	<ul style="list-style-type: none"> <li>• 50% on paternal transmission<sup>55,94</sup></li> <li>• Risk of SRS on maternal transmission<sup>57,95,96</sup></li> </ul>	–
Deletions involving 11p15	1–2% <sup>55,98</sup>	No <sup>55</sup>	Dependent on extent and position of CNV, and parent of origin <sup>55</sup>	–
Mosaic paternal unidiploidy (genome-wide paternal UPD)	Up to 10% of upd(11)pat <sup>62–67,184</sup>	Yes <sup>62–67,184</sup>	Low <sup>62–67,184</sup>	High frequency of neoplasia <sup>63,64,137,152</sup>
MLID	33% of IC2 LOM cases <sup>75–78,88</sup>	Yes <sup>78,88–91</sup>	Low unless an in trans genetic variant is identified <sup>79,80</sup>	Unclear <sup>75,76,78,89,92,93</sup>

DMR, differentially methylated region; dup(11)(p15.5)pat, duplication of paternal 11p15.5; GOM, gain of methylation; LOM, loss of methylation; MLID, multilocus imprinting disturbance; SNV, single nucleotide variation; UPD, uniparental isodisomy; upd(11)pat, paternal uniparental isodisomy of 11p15.5.

phenotypes and recurrence risks that are associated with smaller CNVs within either the telomeric or centromeric domain can be complex, as it depends on their size and the genes and regulatory elements involved<sup>55,99–104</sup>.

Internal IC1 CNVs and SNVs have recurrence risk as high as 50% when occurring on the maternal allele, although incomplete penetrance and possible anticipation have been observed in some cases<sup>73,105,106</sup>. Rare familial cases of BWSp-MLID might be caused by maternal-effect gene mutations (for example, *NLRP2* or *NLRP5* mutations) and might be associated with a very high recurrence risk<sup>79,80</sup>. In the patients that harbour other molecular defects, the recurrence risk is generally low (TABLE 3).

### Prenatal molecular diagnosis

Prenatal testing for BWSp poses particular challenges because, in addition to general aspects of molecular testing (such as the range of molecular disturbances, the challenge of mosaicism detection and the technical limitations of testing), the reliability and informative value of prenatal test results and the ethical issues involved must be considered before sampling<sup>107</sup>.

The major indications for prenatal diagnosis of BWSp are familial cases with a known genetic alteration and a high recurrence risk and patients with no family history in which possible features of BWSp (usually exomphalos but also macrosomia, hemihypertrophy, organomegaly

and polyhydramnios) have been detected using prenatal fetal ultrasonography (TABLE 2, R18). The diagnostic testing for prenatal samples does not therefore necessarily follow the same flow as that for postnatal samples but reflects the individual situation (TABLE 2, R19).

Although chorionic villus (CVS) cells, amniotic fluid cells or fetal blood cells (native and cultured) might be used for molecular testing, it is possible that cell culture might influence the methylation patterns<sup>108</sup>. In CVS cells, the methylation pattern at 11p15.5 might be different from that of embryonic tissues<sup>108</sup>, and/or CVS cells might not reflect the (epi)genetic constitution of the fetus, and therefore, false-positive results might occur<sup>107</sup>. False-negative prenatal test results might occur with all types of testing owing to mosaicism; therefore, a normal prenatal test result cannot absolutely exclude a diagnosis of BWSp (TABLE 2, R20). Because of the fairly recent adoption of prenatal testing and the challenges involved, it is recommended that multicentre audit of cases, methods and diagnostic rates be implemented prospectively, to enable ongoing refinement of best practice guidelines (TABLE 2, R21).

### Care and management aspects of BWSp

In view of the complex multisystem manifestations of BWSp, the consensus group recognized the requirement for effective coordination of health care (TABLE 4, R22).

Table 4 | Recommendations of the management working group

R	Recommendation	Strength of recommendation
22	It is recommended that each patient with BWSp should have an experienced lead health-care provider who will organize the referral to each specialist and will coordinate care for the patient	A+++
<b>Prenatal management</b>		
23	If a diagnosis of BWSp is suspected or confirmed in the prenatal period, then potential BWSp-related fetal and maternal complications (for example, fetal congenital anomalies, shoulder dystocia from macrosomia, postnatal hypoglycaemia and maternal preeclampsia) should be anticipated and appropriate clinical care should be performed	A+++
24	If a diagnosis of BWSp is suspected or confirmed in the prenatal period, then delivery should take place in a clinical facility where neonatal intensive care can be provided	A+++
<b>Growth and lateralized overgrowth</b>		
25	Growth charts from BWSp patients are needed	A+++
26	Physicians should be aware of the rare possibility of final height >2 SDS above the mean. Postnatal growth and pubertal development should be monitored at least annually until the end of growth	A++
27	Appropriate interventions might be proposed in the case of possible tall stature with the same procedures as for other patients with tall stature	A++
28	Monitoring of leg length discrepancy should be based on clinical examination	A++ (LO)
29	Patients with BWSp should be monitored for LLD at least annually during childhood and referred to a paediatric orthopaedic surgeon if LLD is present	A+++ (LO)
30	Shoe-lifts might be indicated for LLD <2 cm. Epiphysiodesis is usually indicated for predicted LLD >2 cm. Reversible epiphysiodesis might be preferred	A++ (LO)
31	Lengthening of the shorter normal limb should be considered only for specific cases	A+++ (LO)
32	Surgical correction of asymmetric overgrowth of the upper limbs is generally not indicated	A+++ (LO)
<b>Management of macroglossia</b>		
33	If substantial airway obstruction is suspected, a careful evaluation including sleep studies (polysomnography) and/or pulmonologist consultation and ear, nose and throat consultation should be performed	A+++
34	Tongue reduction surgery should be considered usually after the age of 1 year if there are macroglossia-associated feeding problems, persistent drooling, speech difficulties, dental malocclusion and psychosocial problems caused by the altered appearance	A+++
35	Surgical intervention (adenoid tonsillectomy with or without tongue reduction surgery) should be considered earlier in cases of severe airway obstruction	A+++
36	In cases of feeding difficulties, support from feeding specialists and dietetics should be proposed	A+++
37	Tongue reduction surgery should be performed by an experienced surgical team after detailed assessment by a multidisciplinary team (including paediatric anaesthesiologists, intensive care unit members, surgeons, speech therapists and orthodontists), preferably in a reference centre	A+++
38	The results of surgery should be carefully audited, and postoperative follow-up should continue until age 16 years	A+++
<b>Management of exomphalos</b>		
39	Treatment of exomphalos in the context of BWSp should be in accordance with general recommendations for the treatment of exomphalos; however, in BWSp-associated cases, attention should be paid to the risk of hypoglycaemia and the anaesthetic risks associated with severe macroglossia	A+++
<b>Management of hypoglycaemia</b>		
40	Capillary blood glucose should be monitored in neonates with a clinical suspicion or confirmed diagnosis of BWSp for the first 48 hours of life. Hypoglycaemia should be defined by two consecutive (30 min) glucose levels <50 mg/dl (<2.75 mmol/l) during the first 6 hours of life or <60 mg/dl (<3.5 mmol/l) later. In case of hypoglycaemia, the newborn baby should be transferred to a neonatal intensive care unit	A++
41	A diagnostic fasting test (including measurement of glucose, insulin and ketones after 6 hours of fasting for full-term babies and after 4 hours for preterm babies) should be performed 48 hours after birth and before discharge from the nursery for neonates with a suspicion of BWSp	A++
42	No specific management of hyperinsulinism and/or hypoglycaemia has been proposed in the context of BWSp, and management of hyperinsulinism and/or hypoglycaemia should be performed according to general recommendations	A++
43	In case of severe persistent hyperinsulinism in a patient with BWSp, additional causes of hyperinsulinism should be investigated	A+++
<b>Management of cardiac lesions</b>		
44	Physicians should be aware of the increased prevalence of cardiac anomalies in children with BWSp	A++
45	A baseline, clinical cardiovascular examination should be performed at diagnosis in all children with clinical and/or molecular diagnosis of BWSp. Individuals with clinically detected or suspected cardiovascular abnormalities should be referred for specialist cardiac assessment and echocardiography	A+++



Table 4 (cont.) | **Recommendations of the management working group**

R	Recommendation	Strength of recommendation
<b>Management of cardiac lesions (cont.)</b>		
46	Annual evaluation and electrocardiogram are recommended in patients with genomic rearrangements involving the IC2 region	B+
47	Management and follow-up of congenital cardiac lesions (for example, ventricular septal defect) should be as in the population without BWSp	A+++
<b>Management of neurological features</b>		
48	Cognitive development should be monitored by the paediatrician. Particular attention should be paid to those with risk factors such as preterm birth and neonatal hypoglycaemia and to carriers of chromosome rearrangements or paternal genome-wide UPD	A+++
49	For patients with a clinical diagnosis of BWSp and a learning disability with no molecular or chromosomal anomaly, other potential diagnoses should be considered and excluded ( <a href="#">Supplementary information S3</a> (table))	A+++
50	Neurological investigations, including MRI, might be indicated only in children with neurological symptoms	A++
<b>Management of renal complications</b>		
51	At diagnosis of BWSp, all patients should be screened for nephro-urological malformations by clinical evaluation and USS	A+++
52	Physicians should be aware of the possibility of hypercalciuria, which can lead to nephrocalcinosis	A++
53	Patients with USS-detected anomalies should be referred to a paediatric nephrologist and urologist for specific follow-up	A+++
54	For patients undergoing abdominal surveillance for tumour screening, physicians and radiologists should pay attention to the possibility of nephrocalcinosis and/or stones	A+++
55	For patients with BWSp, at the time of adult transition, a nephro-urological evaluation (clinical examination, blood pressure and USS) should be performed	A++
<b>BWSp and embryonal tumours</b>		
56	Screening should be stratified according to the genotype	A+++
57	Abdominal USS for BWSp-related tumours every 3 months until age 7 years is recommended for all patients with BWSp except patients with isolated IC2 LOM	A++
58	For patients with BWSp and upd(11)pat, abdominal USS for Wilms tumour and hepatoblastoma every 3 months until age 7 years is recommended	A+++
59	For patients with BWSp and IC1 GOM, abdominal USS for Wilms tumour every 3 months until age 7 years is recommended	A+++
60	For patients with BWSp and IC2 LOM, no tumour surveillance is recommended	*A/B+
61	For patients with BWSp and a CDKN1C mutation, abdominal USS for neuroblastoma every 3 months until age 7 years is recommended	A+
62	For patients with BWSp and an 11p15 duplication, abdominal USS for Wilms tumour every 3 months until age 7 years is recommended	A+++
63	For patients with classical BWS without a molecular defect, abdominal USS every 3 months until age 7 years is recommended	A++
64	α-Fetoprotein (AFP) screening is not recommended for patients with BWSp	A+
65	Catecholamine screening is not recommended for patients with BWSp	A+++
66	There should be a lower threshold for investigation in cases of possible tumour-related symptoms or in response to parental concerns	A+++
67	Treatment of tumours in patients with BWSp might be different from treatment of patients with sporadic diseases and should be discussed with respective study groups unless specific BWSp recommendations are given in the relevant tumour treatment protocols	A+++
<b>Late-onset complications</b>		
68	Individuals with BWSp should be reviewed at age 16–18 years to identify any complications that will require continued follow-up by adult health-care services	A+++
69	Young adults with BWSp should be alerted to the availability of genetic counselling so that they can seek advice prior to starting a family	A+++
70	Given the paucity of data on the long-term health effects of a diagnosis of BWSp, further research should be undertaken	A+++
<b>Psychological and counselling aspects</b>		
71	Health professionals caring for children and families with BWSp should take a holistic approach to care and be prepared to offer referral to specialist counselling and family support services as required. Especially, psychological evaluation and support should be offered to children and their families if required	A+++
72	When the clinical diagnosis is confirmed, parents should be offered the contact details of BWSp support groups	A+++

BWSp, Beckwith–Wiedemann spectrum; GOM, gain of methylation; LLD, leg length discrepancy; LO, lateralized overgrowth; LOM, loss of methylation; SDS, standard deviation scores; UPD, uniparental isodisomy; upd(11)pat, paternal uniparental isodisomy of 11p15.5; USS, ultrasound scan. \*Equal numbers of participants chose option A and option B.

### Prenatal management

In patients with BWSp for whom a risk of recurrence has been identified (TABLE 3), some parents might wish to consider prenatal diagnosis. If a molecular diagnosis is not available or indicated, then ultrasonographic detection of an anterior abdominal wall defect or macroglossia or, less specifically, macrosomia, visceromegaly, polyhydramnios, placentomegaly or pancreatic overgrowth might indicate a likely diagnosis of BWSp<sup>109</sup>. Rarer manifestations detectable by prenatal ultrasound scan (USS) include placental mesenchymal dysplasia, urinary tract abnormalities, cardiac defects, adrenal cysts and masses<sup>110,111</sup>. Abnormal prenatal biochemical screening results — for example, elevated levels of free  $\beta$ -human chorionic gonadotropin in the first trimester<sup>109–111</sup> and/or increased  $\alpha$ -fetoprotein (AFP) levels in the second trimester (associated with exomphalos)<sup>112</sup> — can be associated with BWSp in the fetus. In pregnancies known to be at increased risk of BWSp, the presence of a single anomaly (for example, exomphalos) might be sufficient to make a presumptive diagnosis.

In pregnancies without a previous history of BWSp, none of the prenatally detectable features of BWSp are, in isolation, pathognomonic. Approximately 10–20% of fetuses with a prenatally diagnosed isolated exomphalos<sup>112,113</sup> and ~20% of those with placental mesenchymal dysplasia<sup>114</sup> will have BWSp. As cytogenetic and/or chromosome microarray analysis are indicated for both these findings, molecular analysis for BWSp can also be performed on the same sample, and confirmation or exclusion of BWSp might be helpful for the parents. For less-specific features (for example, urinary tract abnormalities and cardiac defects), testing for BWSp is likely to depend on whether there are multiple BWSp-related features present.

When a prenatal diagnosis of BWSp is suspected or confirmed, the management of individual congenital anomalies (for example, exomphalos or cardiac defect) generally follows standard protocols based on usual local practices. However, macrosomia might cause problems (for example, shoulder dystocia) at delivery, and therefore, growth should be carefully monitored in the latter stages of pregnancy and appropriate arrangements for delivery should be made (TABLE 4, R23,24). BWSp is also associated with polyhydramnios and premature birth. Potential post-delivery complications such as neonatal hypoglycaemia, respiratory obstruction from macroglossia, surgical repair of exomphalos and so on should be anticipated, and appropriate monitoring and facilities should be put in place.

Maternal complications associated with a diagnosis of fetal BWSp include gestational hypertension (~2.4-fold increased risk) and pre-eclampsia<sup>115,116</sup>. In addition, haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome has been reported occasionally in BWSp<sup>116,117</sup>. Therefore, in cases of a suspicion of fetal BWS, such a condition should be looked for with a lower threshold than with normal pregnancies.

### Growth and lateralized overgrowth

Although prenatal and postnatal overgrowth have been considered to be cardinal features in previous reports, overgrowth occurs in only 43–65% of patients<sup>118</sup>. Overgrowth

at birth might be relatively more common in patients with IC1 GOM and segmental pat(11)upd than in other molecular subgroups<sup>14,17</sup>. Postnatal growth is generally in the upper part of the normal range but usually slows in late childhood, and differences in growth trajectories between children with BWSp and those without it should be considered when making predictions of adult height. However, growth trajectories have not been well reported in patients with BWSp, and specific growth charts are needed (TABLE 4, R25). Although few data on final adult height are available, one study reported that final adult height was higher than parental target height, with a mean distance to target height of  $1.7 \pm 1.1$  SDS and approximately one-half of the patients having height SDS >2 (REF. 15) (TABLE 4, R26). Advanced bone age is infrequent (~3%)<sup>119,120</sup>, and to date, there are no data regarding treatment of tall stature in cohorts of patients with BWSp (TABLE 4, R27).

Lateralized overgrowth might occur in all molecular subtypes of BWSp, but it is rare in patients with a *CDKN1C* mutation and is the most frequent feature in patients with segmental upd(11)pat<sup>11,14</sup>. Molecular abnormalities in region 11p15 might be observed in patients with isolated lateralized overgrowth, which enables a diagnosis of BWSp in such cases<sup>119,121</sup>. Leg length discrepancy (LLD) can be associated with substantial morbidity and can negatively influence quality of life<sup>122</sup>. The management of LLD will depend on severity (TABLE 4, R28–31). Shoe-lifts might be indicated for LLD <2 cm. As in isolated (non-BWSp) LLD, epiphysiodesis might be considered for LLD discrepancy >2 cm (REF. 123) (TABLE 4, R30). Surgical correction of asymmetric overgrowth of the upper limbs is generally not indicated (TABLE 4, R32).

### Management of macroglossia

Of children diagnosed with classical BWS, 90% have macroglossia, and BWSp is the most common cause of macroglossia in childhood<sup>124</sup>. Although macroglossia might appear to regress spontaneously in some children (from a combination of a decrease in growth velocity and an increase in growth of the mandible), ~40% of children with BWS undergo a surgical tongue reduction<sup>125</sup>. The most common indications for surgery are problems with feeding; persistent drooling; difficulties with articulation; orthodontic problems, including prognathism and development of an anterior open-bite and incisor spacing and/or flaring; and psychosocial difficulties resulting from abnormal cosmetic appearance and difficulties with speech, feeding and drooling<sup>126–128</sup> (TABLE 4, R33–35).

The enlarged tongue is usually increased in size in all three dimensions, and the aim of surgery is to reduce the tongue bulk while preserving normal shape and improving function. The most common surgical approach is anterior wedge resection, but a variety of other techniques have been described<sup>125,128,129</sup>. Surgical complications, although infrequent, can include postoperative oedema of the tongue and wound dehiscence.

In rare cases, respiratory problems might require surgery to be performed in the neonatal period, and preoperative tracheostomy might be required<sup>125</sup>. When obstructive sleep apnoea is suspected, an airway evaluation and

appropriate further investigation with polysomnography can be used for objective assessment<sup>130,131</sup> (TABLE 4, R33). In the absence of respiratory obstruction, surgery is generally delayed until at least age 12 months (when tongue size is more stable) (TABLE 4, R34). If the indication for surgery is unclear, the child's progress should be monitored to determine whether indications arise in the future. Long-term follow-up studies generally show favourable results of surgery in most cases, with cosmetic improvement, reduced drooling, resolution of feeding difficulties, improved speech, adequate tongue mobility and, usually, no substantial effect on taste sensation<sup>126–128</sup>. Surgery has been reported to provide good outcomes in children who are operated on at a wide variety of ages but mainly in those who are operated on before 2–3 years<sup>125,127</sup>.

To facilitate objective assessments and accrual of accurate long-term prognostic data, surgery should, whenever possible, be restricted to a small number of units that can offer a multidisciplinary service (including an experienced surgical team) and long-term follow-up (TABLE 4, R35–38).

## Management of exomphalos

Exomphalos is a cardinal feature of BWSp (BOX 2) and is preferentially associated with molecular defects occurring within the centromeric domain (IC2 LOM or *CDKN1C* mutations)<sup>11,14,17</sup>. To date, no specific recommendations have been given regarding the management of exomphalos occurring in patients with BWSp compared with isolated exomphalos in accordance with usual local practices (TABLE 4, R39).

Molecular investigations of apparently isolated exomphalos in neonates rarely detect a molecular abnormality in the absence of additional BWSp features<sup>132</sup>.

## Management of hypoglycaemia

Hypoglycaemia in BWSp is due to excess insulin and occurs in 30–60% of children with BWSp<sup>11,14,17</sup>. Although BWSp-related neonatal hypoglycaemia is often transient and resolves within a few days, in up to 20% of neonates, it can persist beyond the first week of life and require medical treatments or even pancreatectomy in the most severe cases<sup>20</sup>.

Congenital hyperinsulinism is a rare condition with a range of causes<sup>20,133</sup>. In a cohort of 501 patients with hyperinsulinism (excluding patients with focal hyperinsulinism), ~6% had features of BWSp (most of whom had segmental upd(11)pat), and half of these patients underwent surgery owing to persistent hypoglycaemia after optimal medication<sup>27</sup>.

Although low plasma glucose concentrations are common during the first 24 hours of life in all neonates, by day 3, plasma glucose concentrations in neonates are similar to those of older children, with a normal range of 3.5–5.5 mmol/l (60–100 mg/dl)<sup>134</sup>. A diagnosis of hyperinsulinism is based on evidence of increased insulin secretion and/or actions at the time of hypoglycaemia, including a detectable insulin level, suppressed levels of plasma  $\beta$ -hydroxybutyrate (ketones), suppressed levels of plasma free fatty acids and a glycaemic response

to glucagon. Diagnosis should be made in consultation with an endocrinologist who is familiar with hyperinsulinism.

Neonates with suspected BWSp should be screened for hypoglycaemia (TABLE 4, R40,41) before discharge from the nursery. Neonates with confirmed hypoglycaemia should be treated to maintain a plasma glucose concentration >3.9 mmol/l (>70 mg/dl)<sup>134</sup>. Management of hyperinsulinism includes medical therapies such as diazoxide and somatostatin analogues (such as octreotide and lanreotide). Surgery (pancreatectomy) might be indicated if persistent hypoglycaemia occurs despite maximal medical therapies<sup>135</sup>. New therapies such as mechanistic target of rapamycin (mTOR) inhibitors (sirolimus) or glucagon-like peptide 1 receptor (GLP1R) antagonists have been used in the treatment of hyperinsulinism and very recently in BWSp<sup>136</sup>; however, to date, no specific management (medical or surgical) for hyperinsulinism has been evaluated in the context of BWSp (TABLE 4, R42).

Two genes that are implicated in congenital hyperinsulinism, *ABCC8* and *KCNJ11*, map to chromosome 11p, and some patients with BWSp might carry a heterozygous mutation in either gene<sup>27</sup>, although these are rare. If these genes are included in the isodisomy, then homozygosity for the mutation in disomic cells produces severe hypoglycaemia<sup>27</sup>. In cases of hypoglycaemia with hyperinsulinism and without other traits suggestive of BWSp, investigations for 11p15.5 methylation abnormalities might be considered.

## Management of cardiac lesions

Congenital heart disease is more prevalent in BWS than in the general paediatric population, and cardiac defects occur in up to 13–20% of patients with BWS<sup>12,17,23</sup> (TABLE 4, R44). Minor anatomical defects (for example, cardiomegaly, patent ductus arteriosus or patent foramen ovale and interatrial or interventricular defects) require echocardiographic monitoring until usual spontaneous resolution occurs (TABLE 4, R45). More severe defects might require surgical correction, although the management will be similar to that in sporadic cases of heart disease (TABLE 4, R47).

Congenital long QT syndrome has been reported in two families with BWS harbouring an intragenic deletion and a translocation at IC2 leading to inactivation of the *KCNQ1* gene, which, although very rare, is associated with a risk of sudden death<sup>85,102</sup> (TABLE 4, R46).

## Management of neurological features

Cognitive development is usually normal in patients with BWSp; however, developmental delay can be associated with prematurity, severe hypoglycaemia, unbalanced chromosome rearrangements or paternal genome-wide UPD<sup>137</sup> (TABLE 4, R48). The differential diagnosis should be carefully considered in patients with presumptive BWS and learning disability and without an 11p15 anomaly, as some overgrowth disorders (for example, Sotos syndrome, Malan syndrome and Simpson–Golabi–Behmel syndrome) are more frequently associated with developmental delay<sup>30,138–144</sup> (TABLE 4, R49; see [Supplementary information S3](#) (table)).

Malformations of the central nervous system (for example, abnormal posterior fossae (including Dandy–Walker malformations) or abnormal corpus callosum or septum pellucidum) have been reported in rare patients with BWSp (chiefly with a defect involving IC2)<sup>83,145</sup>, and these features might need to be considered in children with neurological symptoms or signs (TABLE 4, R50).

### Management of renal complications

The prevalence of nephro-urological anomalies in BWSp is 28–61%<sup>146</sup>. A variety of anomalies have been described; cortical and medullary cysts occur in ~10% of patients with BWSp and the prevalence of hypercalcaemia and nephrolithiasis is increased compared with that in the general population<sup>147</sup>. Although not all nephro-urological anomalies detected by ultrasonography will be of clinical importance, a minority of anomalies might be severe (and usually detectable prenatally) and require medical or surgical management. Severe vesicoureteral reflux might cause kidney damage and recurrent urinary tract infections<sup>148</sup>. In addition, nephromegaly might be a marker of increased risk of Wilms tumour<sup>146</sup>.

Renal anomalies might occur in all molecular subtypes of BWSp, but only certain groups might be offered regular renal imaging for tumour surveillance. Management of the nephro-urological aspects of BWSp should be pragmatic and balance the benefits of presymptomatic diagnosis and treatment of critical obstructions and urinary tract infections for preserving renal function with the drawbacks of over-investigation for benign variants detected by surveillance. Thus, we recommend a nephro-urological evaluation at clinical diagnosis and at the time of adult transition for any patient with BWSp and screening for nephrocalcinosis and/or stones in only patients who undergo abdominal USS for tumour screening (TABLE 4, R51–55).

### BWSp and embryonal tumours

Embryonal tumours occur in ~8% of children with BWSp<sup>149</sup>. The most common types of embryonal tumours are Wilms tumour (52% of all tumours), hepatoblastoma (14% of all tumours), neuroblastoma (10% of all tumours), rhabdomyosarcoma (5% of all tumours) and adrenal carcinoma (3% of all tumours)<sup>14</sup>. Although there are some differences in mean age at diagnosis between tumour types, the overall cancer risk is highest in the first 2 years of life, and clinical experience suggests that the cancer risk then declines progressively before puberty, approaching the cancer risk of the general population. Currently, there is no evidence of an increased risk of malignant tumours in adulthood ([Supplementary information S4](#) (table)).

The tumour risk correlates with the BWSp molecular subgroup; patients with segmental upd(11)pat and IC1 GOM have a higher tumour risk than patients with *CDKN1C* mutations and IC2 LOM<sup>58</sup>. The four main molecular subgroups are characterized by a cancer risk gradient, with the highest risk in cases of IC1 GOM (28% risk), followed by segmental upd(11)pat (16% risk), *CDKN1C* mutation (6.9% risk) and IC2 LOM (2.6% risk)<sup>14</sup>. In addition, there are also differences in the

tumour types observed between molecular subgroups. Patients with IC1 GOM are mostly predisposed to developing Wilms tumour (observed in 24% of patients and accounting for 95% of malignancies in this group)<sup>14,15,149</sup>. Conversely, patients with IC2 LOM and *CDKN1C* mutations do not usually develop Wilms tumour but rather develop other tumours such as hepatoblastoma, rhabdomyosarcoma and neuroblastoma. Thus, a study from 2016 reported a prevalence of Wilms tumour of ~0.2% (2/995) in patients BWSp and IC2 LOM<sup>149</sup>; although a report from 2017 suggested that the risk of Wilms tumour in patients with IC2 LOM is underestimated, only a single patient with Wilms tumour and an IC2 epimutation was observed<sup>150</sup>. Therefore, when put together with previous reports of Wilms tumour in large cohorts of patients with BWSp, the overall prevalence of Wilms tumour with IC2 LOM is probably well below 1%<sup>151</sup>. Patients with *CDKN1C* mutations are mostly predisposed to neuroblastoma<sup>14,15,149</sup>. Patients with segmental upd(11)pat are predisposed to develop any of the tumour types seen in BWSp (TABLE 5). Individuals with genome-wide paternal UPD seem to have a high risk of developing tumour types similar to those with segmental upd(11)pat but with an increased incidence of hepatic and/or adrenal tumours extending into adolescence and young adulthood<sup>63,64,137,152</sup>.

Specific studies investigating the tumour risk in patients with isolated lateralized overgrowth and clinically diagnosed BWS with negative molecular testing are lacking. It seems plausible that the cancer risk in patients with isolated lateralized overgrowth who fall within the BWSp is linked to the type of 11p15.5 molecular anomaly. Indeed, the tumour risk in patients with isolated lateralized overgrowth and segmental upd(11)pat is estimated to be as high as 32–50%<sup>121,153</sup>.

### Tumour surveillance strategies

Tumour screening in patients with inherited cancer predisposition syndromes aims to improve patient survival and reduce morbidity through earlier detection of tumours. However, no surveillance protocol can detect every tumour, and there are both benefits and drawbacks to screening — the latter include the financial costs, morbidity that can result from investigating asymptomatic benign lesions detected on surveillance and psychosocial burden of repeated investigations for the patient and family. There is no generally accepted risk threshold for instigating tumour screening strategies, and it might vary according to regional medical and medicolegal practices and local health-care systems. Although screening is considered for a tumour risk >1% in the USA, a risk of 5% might be considered an appropriate threshold in Europe<sup>10,154</sup>. Various protocols have been suggested for tumour surveillance in BWSp, usually comprising abdominal USS with or without measurement of AFP levels at various ages and intervals during infancy<sup>14,15,155</sup>. Traditionally, although most protocols have been applied to all cases of BWSp, the definition of specific epigenotype–tumour risk correlations provides a basis for more targeted surveillance protocols.



Table 5 | Proposed tumour surveillance protocol for Beckwith–Wiedemann spectrum

Tumour risk (% of patients)*	Tumour type for surveillance	Surveillance procedures	Timing
<b>IC2 LOM</b>			
<ul style="list-style-type: none"> <li>• Overall risk (2.6%)</li> <li>• Hepatoblastoma (0.7%)</li> <li>• Rhabdomyosarcoma (0.5%)</li> <li>• Neuroblastoma (0.5%)</li> <li>• Thyroid cancer (0.3%)</li> <li>• Wilms tumour (0.2%)</li> <li>• Melanoma (0.1%)</li> </ul>	Tumour incidence lower than other molecular subgroups; extremely variable tumour spectrum; only half of tumours arise in the abdomen	<ul style="list-style-type: none"> <li>• No routine USS surveillance</li> <li>• Clinical assessment and USS in response to signs and/or symptoms or parental concerns</li> </ul>	–
<b>IC1 GOM</b>			
<ul style="list-style-type: none"> <li>• Overall risk (28.1%)</li> <li>• Wilms tumour (24%)</li> <li>• Neuroblastoma (0.7%)</li> <li>• Pancreatoblastoma (0.7%)</li> </ul>	Wilms tumour	Abdominal USS	Every 3 months from diagnosis until age 7 years
<b>upd(11)pat</b>			
<ul style="list-style-type: none"> <li>• Overall risk (16%)</li> <li>• Wilms tumour (7.9%)</li> <li>• Hepatoblastoma (3.5%)</li> <li>• Neuroblastoma (1.4%)</li> <li>• Adrenocortical carcinoma (1.1%)</li> <li>• Pheochromocytoma (0.8%)</li> <li>• Lymphoblastic leukaemia (0.5%)</li> <li>• Pancreatoblastoma (0.3%)</li> <li>• Hemangioma (0.3%)</li> <li>• Rhabdomyosarcoma (0.3%)</li> </ul>	<ul style="list-style-type: none"> <li>• Wilms tumour</li> <li>• Hepatoblastoma</li> <li>• Adrenal tumours</li> </ul>	Abdominal USS	Every 3 months from diagnosis until age 7 years
<b>CDKN1C mutation</b>			
<ul style="list-style-type: none"> <li>• Overall risk (6.9%)</li> <li>• Wilms tumour (1.4%)</li> <li>• Neuroblastoma (4.2%)</li> <li>• Acute lymphoblastic leukaemia (1.4%)</li> </ul>	Neuroblastoma	Abdominal USS	Every 3 months from diagnosis until age 7 years
<b>Classical BWS with negative molecular tests</b>			
<ul style="list-style-type: none"> <li>• Overall risk (6.2%)</li> <li>• Wilms tumour (4.1%)</li> <li>• Neuroblastoma (0.6%)</li> <li>• Hepatoblastoma (0.3%)</li> <li>• Rhabdomyosarcoma (0.3%)</li> <li>• Adrenocortical carcinoma (0.3%)</li> </ul>	Wilms tumour	Abdominal USS	Every 3 months from diagnosis until age 7 years

Proposed tumour surveillance protocols for patients with Beckwith–Wiedemann spectrum (BWS) disorder (including those with isolated lateralized overgrowth who have 11p15 abnormalities) are shown and stratified according to molecular subtype. Although there are differences in tumour risks and prevalent tumour types between molecular subgroups when surveillance is recommended, a single surveillance programme is used to reduce confusion and enhance consistency. In specific health-care systems, practice might currently vary from this protocol (see the main text for details). BWS, Beckwith–Wiedemann syndrome; GOM, gain of methylation; LOM, loss of methylation; upd(11)pat, paternal uniparental isodisomy of 11p15.5; USS, ultrasound scan. \*Tumour and histotype prevalence data from Maas *et al.*<sup>14</sup> and Mussa *et al.*<sup>17</sup>; 7 years refers to the risk of Wilms tumour, as hepatoblastoma usually occurs before age 2 years.

**Screening for Wilms tumour.** Abdominal USS is the preferred modality for Wilms tumour screening. The doubling time of Wilms tumour cells has been estimated to be 11–13 days<sup>156</sup>, and USS is recommended every 3–4 months<sup>157,158</sup>. Given the high survival of individuals with Wilms tumour (90% overall survival at 4 years), early detection of Wilms tumour by surveillance is predicted to only marginally impact survival; however, diagnosis at an earlier stage might reduce the burden of treatment-related morbidity<sup>159–162</sup>.

If Wilms tumour screening is targeted by BWS molecular subgroup, patients with IC1 GOM and segmental upd(11)pat are at the highest risk, and several groups have suggested that patients with IC2 LOM should not be screened using USS in order to avoid excessive medicalization and possible false-positive results<sup>149,154</sup>.

**Screening for hepatoblastoma.** The risk of hepatoblastoma in patients with BWS is >2,000-fold higher than in the general population, and hepatoblastoma is the second most common tumour type in BWS<sup>21</sup>. However, specific studies evaluating hepatoblastoma screening in BWS are lacking. Abdominal USS is a first-line investigation in children with a suspected liver mass, although not all parts of the liver can be imaged easily and small tumours might be missed<sup>159</sup>. Concerns about the sensitivity of abdominal USS led to suggestions that it should be combined with measurements of serum levels of AFP, which is secreted by >95% of hepatoblastomas<sup>163–165</sup>. Treatment and outcome of patients with hepatoblastoma are closely connected to tumour stage at diagnosis, and preliminary data suggested that patients with BWS and hepatoblastoma who are screened for AFP have an earlier stage at diagnosis and a better

prognosis than unscreened patients and that increased serum AFP levels might precede hepatoblastoma detection by USS<sup>166</sup>. However, this hypothesis is unproved, and further data are required. In the paediatric setting, interpreting serum AFP levels can be complex owing to the wide range and variable concentrations in early infancy<sup>167,168</sup>. Serum AFP levels might be higher in babies with BWSp and without hepatoblastoma than in age-matched healthy controls<sup>169</sup>. In view of the burden of repeated venepuncture and the complexity of interpreting elevated AFP levels, it has been debated whether the benefits of AFP screening in BWSp outweigh the drawbacks<sup>170–173</sup>, and the consensus voted not to recommend AFP screening (TABLE 4, R64).

**Screening for neuroblastoma.** Although reported in all BWSp molecular subgroups, neuroblastomas are preferentially associated with *CDKN1C* mutations, with a frequency of ~4%<sup>14</sup> (TABLE 5). Detection of asymptomatic neuroblastomas by determination of the urinary tumour markers vanillylmandelic acid and homovanillic acid and/or the catecholamine to creatinine ratio combined with three monthly USSs until age 2–3 years has been suggested<sup>149</sup>. However, previous neuroblastoma screening strategies using urinary markers in large-scale paediatric settings had a very minor influence on the related morbidity and mortality<sup>174,175</sup>, and there is currently no evidence that neuroblastoma screening in BWSp improves treatment and survival (TABLE 4, R65).

**Surveillance for other tumour types.** Screening for adrenal carcinoma can be undertaken using clinical evaluation, adrenal USS and determination of serum dehydroepiandrosterone sulfate concentrations every 4–6 months<sup>176</sup>. However, adrenal carcinoma is rare in BWS (even in patients with genome-wide paternal UPD, who are at the highest risk), and there is no data on the utility of such screening strategies in BWSp.

#### Consensus tumour surveillance protocol

The consensus group agreed that tumour surveillance should be targeted to those molecular subgroups of BWSp that are at highest risk and that children with BWSp and IC2 LOM should not be offered routine USS (TABLE 4, R60) (although, there should be a low threshold for investigation in response to symptoms or parental concern). Other BWSp molecular subgroups and patients with classical BWS and no detectable molecular anomaly should be offered abdominal USS every 3 months until age 7 years (TABLE 4, R57–59, 61–63; TABLE 5). It was agreed that AFP measurements should not be offered routinely because the incidence of hepatoblastoma was judged too low to warrant specific screening, the influence of surveillance of patients and families is unclear, and the difficulties in interpretation might lead to false-positive results (TABLE 4, R64). Nevertheless, in specific health-care systems, clinicians might currently vary from the proposed protocol, especially when regional protocols are available, pending the outcome of the results of prospective studies of targeted and universal surveillance.

The consensus surveillance protocol enables ~50% of children with BWSp at low tumour risk to be spared 3 monthly USSs, and although the risk of Wilms tumour, for example, is small in patients with a *CDKN1C* mutation, applying a common surveillance modality (abdominal USS rather than renal USS in some subgroups, liver USS in other subgroups and so on) in all the groups to be screened avoids the potential for confusion with more complicated regimens. It should be noted that the agreed protocol differs from that recommended recently by the American Association for Cancer Research (AACR) Childhood Cancer Predisposition Workshop, which adopted a 1% risk threshold for surveillance and therefore recommended abdominal USS and AFP screening for all cases of BWSp<sup>155</sup>. Both the AACR group and this consensus group made these decisions on the basis of similar data for tumour risks in different molecular subgroups but came to differing conclusions with regard to adopting a targeted screening approach. It should be noted that the AACR group consisted predominantly of experts from North America, whereas the international BWS consensus group was composed predominantly of experts from European centres, where targeted screening has already been adopted in some countries<sup>14,154</sup>. Thus, the difference in screening recommendations between the two groups reflects mainly the different medical and medicolegal cultures in North America and Europe. Although a universally agreed upon screening protocol would usually be preferable, taking into account the different conclusions between the experts of both the AACR group and this consensus group, it is reasonable that at this time, screening protocols could be different between Europe and North America. Such diversity of practice can be helpful, as careful audit of the results of the two protocols can help further refine our recommendations at future international consensus meetings<sup>155</sup>.

#### Management of BWSp-related tumours

Children with BWSp and Wilms tumour, when compared with non-syndromic children with Wilms tumour, present with less metastatic disease because of earlier stage disease, fewer anaplastic tumours and a higher incidence of bilateral synchronous or metachronous recurrence<sup>161</sup> (TABLE 4, R67). The latter seem to be connected to the presence of multifocal or diffuse nephrogenic rests in one or both kidneys (nephroblastomatosis)<sup>177</sup>, a feature that is not easily distinguishable from Wilms tumour on standard imaging<sup>160</sup>. Although patients with BWSp and Wilms tumour who are diagnosed using abdominal USS surveillance have a smaller tumour size than children with sporadic Wilms tumour<sup>157</sup>, overall survival values are similar (at least 90% at 4 years)<sup>161</sup>. Smaller Wilms tumours are more amenable to partial nephrectomy and nephron-sparing strategies (such as partial nephrectomy) are particularly preferred in patients with BWSp given the potential co-occurrence of progressive non-malignant renal diseases and bilateral Wilms tumours<sup>158</sup>. Data from 2016 show comparable outcomes after nephron-sparing surgery and total nephrectomy in patients with BWSp and Wilms tumour<sup>160</sup>.

## **Late-onset complications**

Features of BWSp such as macroglossia and postnatal overgrowth tend to ameliorate with age, and therefore, BWSp is often likely overlooked in adults unless there is a prior diagnosis in childhood. There is a paucity of information on long-term outcomes and late-onset complications in adults with BWSp (TABLE 4, R70). Concerns about potential adult-onset complications that are not directly related to childhood features of BWSp fall into four areas.

**Neoplasia.** Despite the link with embryonal neoplasia, there is no apparent association between BWSp and predisposition to common adult-onset carcinomas. Although rare endocrine tumours have been reported in adults with BWSp<sup>62,152,178–180</sup> (Supplementary information S4 (table)), there is no evidence of a specific tumour risk that might justify surveillance. However, follow-up of large series of adults with BWS has not been performed. Children with BWSp who are treated for embryonal tumours might develop late-onset complications from surgery, radiotherapy or chemotherapy, similar to children with sporadic tumours.

**Cardiovascular defects.** Patients with congenital heart disease require appropriate follow-up in adult specialty clinics. Although rare, cardiovascular defects might be diagnosed for the first time in adulthood<sup>181</sup>, but routine screening is not indicated. Patients with rare IC2 CNVs and/or rearrangements that might predispose to long QT syndrome require follow-up throughout adulthood.

**Infertility.** Although congenital anomalies of the urogenital tract (for example, bicornuate uterus) have been described in BWSp<sup>178,181</sup>, there is no clear evidence of excess fertility problems in women with BWSp. Reduced fecundity has been described in affected males (compared with females)<sup>182</sup>, but the frequency of infertility in men with BWSp is unknown.

**Renal anomalies.** Although examples of the diagnosis of renal anomalies in adults with BWSp have been reported<sup>178</sup>, it is assumed that if renal USS was performed, renal abnormalities would usually be detected in childhood.

Although regular surveillance (for example, echocardiography, renal function testing and evaluation of hearing) has been suggested for adults with BWSp<sup>181</sup>, in the absence of abnormalities detected during childhood surveillance, the detection rate of such investigations in asymptomatic adults with BWSp is likely to be low and could pose problems with health insurance. The consensus group agreed that a detailed clinical review and renal USS (Supplementary information S5 (table)) should be undertaken at age 16 years, and specific recommendations for continued surveillance based on only ongoing problems were agreed upon (TABLE 4, R68). Adults with BWSp should be encouraged to seek genetic counselling advice before starting a family (TABLE 4, R69). At that

stage, any potential concerns about fertility can be reviewed and referrals for further investigation made as appropriate.

## **Psychological and counselling aspects**

The diagnosis of a disorder such as BWSp can have wide-ranging effects on the psychological and social well-being of families. Although the precise effects will vary between families and will be influenced by individual medical and social factors, and considering that each family might face different challenges, it is important that all health-care professionals are aware of the wider non-medical issues that might be relevant to the family (TABLE 4, R71). Information on the psychosocial aspects that might be specific to BWSp is sparse. In many cases, there is no previous relevant family history and the parents are not prepared for the diagnosis. Issues such as tumour risk can be worrying, and it is apparent that differing medical practices and recommendations might cause parental uncertainty and anxiety. A survey of parents of children with BWSp who have macroglossia revealed widespread parental concerns about the 'negative cosmetic appearances' of a large protruding tongue and persistent drooling, which led to strangers staring and questioning whether their children had learning difficulties<sup>128</sup>. Parents are also concerned that this might lead to teasing by other children, and a retrospective questionnaire survey revealed an apparent increase in emotional difficulties and problems with peers in children with BWSp<sup>183</sup>. Health-care professionals should be aware that psychosocial difficulties might occur and should be prepared to refer families to specialists such as genetic counsellors, social workers and psychologists, as appropriate. As support groups can have key roles in helping families adjust to the diagnosis, share their concerns and experiences and obtain the correct care and support, all families should be given the contact details of relevant groups (TABLE 4, R72).

## **Conclusions**

The recommendations of the first international BWS consensus group described in this Consensus Statement provide a framework for improving the diagnosis and management of BWSp. As BWSp is characterized by complex genetics and variable multisystem phenotypes, it is important that a lead clinician is identified for each patient (TABLE 4, R22) to ensure coordination of the numerous aspects of care throughout childhood (Supplementary information S5 (table)). The proposed diagnostic and care pathways are intended to be practical and cost-effective (for example, targeting tumour surveillance to high-risk groups should reduce costs compared with universal surveillance strategies). Nevertheless, in some health-care systems and medico-legal environments, further evidence might be required to shift clinical practice (for example, tumour surveillance in North America). Thus, it is important that implementation of these consensus recommendations be accompanied by prospective audits in order to expand the evidence base for future consensus initiatives.

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